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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,436	07/16/2001	Hermann Wagner	C1041/7010	1340

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,436	WAGNER ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/14/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *104-110 and 112-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *104-110,112-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 104-110 and 112-114 are pending.

The finality of the last action is withdrawn because of the new rejections and objections.

Claim Objections

Claims 107 and 108 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The term "nucleotide analog or derivative" indicates that the claims 107 and 108 are broader than the claim from which the claims depend. The term does not indicate whether the backbone of the sequence is modified or any nucleotide can replace a nucleotide in the sequence and be considered an analog or derivative. The claims do not indicate if the term reads on the structure or function of the oligonucleotide. Thus, the term could embrace an oligonucleotide that comprises a CG dinucleotide even though the claim from which they depend from requires that the oligonucleotide does not comprise a CG dinucleotide.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 104-110 and 112-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the antigenicity to a tumor in a subject having a tumor comprising administering a tumor-specific antigen and an adjuvant, wherein the adjuvant is an oligonucleotide 10-50 nucleotides long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, GGGTG, wherein the oligonucleotide does not comprise a CG dinucleotide, does not reasonably provide enablement for a method of treating a tumor in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims read on using a genus of oligonucleotides comprising a G motif for *in vivo* administration to a genus of vertebrate subjects to treat a genus of tumors. Thus, the claims are considered broad. The claims will therefore be evaluated based upon *in vivo* use of the oligonucleotide.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (United States v. Telectronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather a conclusion reached by many factors. These factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in In Re Wands (see above).

The state of the art at the time the application was filed and currently as exemplified by Lipford et al. (Immunology, 101:46-52, 2000) teaches that poly-guanosine motifs co-stimulate

antigen-reactive CD8 T cells. Lipford teaches that G quartet structures may be involved in T-cell stimulation, because at least four, but not less than four consecutive G bases are conditional for stimulation (page 51).

The applicant provides examples that illustrate the properties of G-motif ODN (pages 24-37). In example 1, several G motifs failed to induce TNF in an *in vitro* culture of J774 cells. Example 6 displays that G motif ODNs fail to interfere with lethal shock syndrome induced by either superantigen or endotoxin. Example 7 indicates that G motifs ODN act as adjuvants for generation of antigen-specific cytotoxic T cells in vivo. Example 8 displays that G-motif (ODN PZ2) induced NK activity *in vivo* in experimental mice. Example 10 displays that single stranded ODN, but not double-stranded ODN co-stimulate T cells in vitro.

With respect to tumor specific antigens, the prior art teaches that as tumor cells grow and die they produce tumor specific antigens (e.g., PSA). See Cancer Medicine: Section 2: Cancer Immunology in PubMed[online] Bethesda, MD USA: United States National Library of Medicine [retrieved on 27 December 2005]. Retrieved from: PubMed. The presence of antibodies to tumor specific antigens is already present in the subject. Tumors have evolved means to resist or hide from immune effector cells with tumor specific antigen. The effectiveness of using tumor specific antigens for treating cancer in a patient is considered unpredictable.

The specification does not provide a working example of treating a tumor in a vertebrate subject using the method steps recited in the claimed invention. The prior art is absent for using an oligonucleotide 10-50 nucleotides long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, GGGTG, wherein the oligonucleotide does not comprise a CG

dinucleotide. The prior art has been directed to stimulating an immune response using an oligonucleotide comprising a CG dinucleotide. The applicant contemplates using the G motif as an adjuvant (page 6). As stated in the specification immune adjuvants are well known in the prior art (page 6). The specification enables the skilled artisan to use the claimed method for increasing antigenicity of tumor cells in a subject to a tumor specific antigen. However, the relevance of this data to the treatment of tumors is unclear at best because neither the applicant nor the prior art provide a correlation or nexus between the obtained studies such as those provided by applicant with results the skilled artisan would reasonably expect to see for treating a tumor in a vertebrate subject using the claimed method. See Leitner et al., Current Pharmaceutical Design, 2001, 7:1641-67. Thus, the specification is not considered enabled for treating a tumor in a subject using the claimed method.

In conclusion, the specification and claims coupled with the art of record, at the invention was made, do not provide sufficient guidance and/or evidence to reasonably enable the full scope of the claimed invention. Given that oligonucleotides wherein any oligonucleotide with a G motif is employed to treat a tumor in a vertebrate subject was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a anti-tumor effect produced by any oligonucleotide cited in the claims, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of treating a tumor using an oligonucleotide comprising a G motif.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 114 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "represents the 3' terminus of the oligonucleotide" in claim 114 is a relative term which renders the claim indefinite. The term "represents the 3' terminus of the oligonucleotide" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of the term is not defined because it is not apparent if the term is referring to the structure of function of the oligonucleotide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 107 and 108 are rejected under 35 U.S.C. 102(e) as being anticipated by Krieg et al (US 6339068).

For the reasons set forth above under claim objections, claims 107 and 108 are broader than the limitation recited in claim 104 and the claims can read on an oligonucleotide comprising a CG dinucleotide.

Krieg teaches a method of enhancing an immune response to a tumor antigen in a subject comprising administering an immunostimulatory nucleic acid and an antigen, wherein the antigen is from a tumor (columns 20 and 93-100).

Claims 107 and 108 are rejected under 35 U.S.C. 102(a) as being anticipated by Wagner et al. (WO98/32462, cited on a PTO-892).

For the reasons set forth above under claim objections, claims 107 and 108 are broader than the limitation recited in claim 104 and the claims can read on an oligonucleotide comprising a CG dinucleotide.

Wagner teaches a method for treating a cancer in an experimental tumor model in a mouse comprising administering an oligonucleotide comprising 5-40 nucleotides and a tumor specific antigen to the mouse (pages 28 and 30-31).

Response to Arguments

Applicant's arguments, see pages 2-6, filed 10/14/05, with respect to the rejection(s) of claim(s) 104-110 and 112-113 under 103(a) rejection have been fully considered and are persuasive because combining a tumor specific antigen with an oligonucleotide that inhibits JNK in cells (which is involved stimulating the immune response) would not be obvious to one of ordinary skill in the art. Therefore, the rejection has been withdrawn. However, upon further

consideration, a new ground(s) of rejection is made in view of the breath of term "nucleotide analog or derivative" in claims 107 and 108.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635